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ORIGINAL RESEARCH

Evaluation of the relationship between serum ferritin and insulin resistance in polycystic ovary syndrome

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ABSTRACT-

Aim: To evaluate the levels of Serum Fasting blood glucose, IR and Serum Ferritin in diagnosed PCOS patients and normal controls.

Material and methods: The current study was conducted in urban tertiary hospital based a Case-control analytic cross-sectional study in Departments of Biochemistry and Gynecology & Obstetrics of Faculty of Medicine and Health Sciences, SGT University, Budhera, Gurugram, India on 160 subjects aged between 18 to 45 years comprising of 80 healthy control and 80 patients with clinically diagnosed cases of PCOS, acted as study group. The blood samples of controls as well as study groups were withdrawn and Clinical evaluation included anthropometry, Hight, Weight, Body Mass Index (BMI) and waist-to-hip ratio (WHR) were calculated. Circulating levels of fasting glucose, insulin resistance, and Serum Ferritin level were determined by Chemiluminescence based immunoassay (CLIA) on fully automated Biochemistry analyzer MAGLUMI 1000.

Results: It is observed that the out of total 160 subjects with both control and study group PCOS patients were included in the study. The age of these control group was ranged from 18 to 45 years, with a mean of 26.23±5.58 years and PCOS study were found 27.76 ±6.54 years. The findings of anthropometric measurements of the subjects of both PCOS syndrome (n=80) and non-PCOS (n=80). As expected, mean levels of BMI, Weight, Height showed marked difference and were statistically significantly increased (P<0.0001) in both the groups. The serum levels of serum Fasting blood glucose level, insulin resistance, and Serum Ferritin were significantly increased (P<0.0001) in subjects with PCOS and without PCOS compared to controls.

Conclusion: These results demonstrated that elevated level of serum ferritin was associated with insulin resistance in PCOS women.

Key words- Serum ferritin, Insulin resistance, Polycystic ovarian syndrome

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a complex and heterogeneous disorder characterized by hyperandrogenemia, hyperinsulinemia, insulin resistance, and chronic anovulation. It is the most common endocrine disorder in women of reproductive age. It is now well-known that PCOS is

associated with insulin resistance and abnormal glucose tolerance and later on type 2 diabetes. Serum ferritin levels are also increased in PCOS patients, suggesting mild iron overload.[1-3]

Factors contributing to potential iron overload in women with PCOS include the iron-sparing effect of chronic anovulation and oligo or amenorrhea, insulin resistance, and a decrease in hepcidin, which leads to increased iron absorption.[2,3] Iron is essential for cell metabolism and is a constituent of hemoproteins, such as hemoglobin, myoglobin, and cytochrome P450, and total body iron levels are precisely regulated under normal physiologic conditions.[4] Ferritin is a ubiquitous intracellular protein that stores iron in cells and its circulating levels serve as a marker for body iron stores.[2] Ferritin is essential for the regulation of iron homeostasis, it is found in proportion to the size of cellular iron stores in absence of other confounding factors.[2] Iron is a strong pro-oxidant, and high body iron levels are associated with an increased level of oxidative stress, which causing inhibition of insulin internalization and actions, results in hyperinsulinemia and insulin resistance.[5,6] In the progression of diabetes excess iron induced free radicals can cause both β cell failure and insulin resistance.[6,7] The first and clearest evidence for a relation between iron and human diabetes was observed in individuals with pathologic iron overload like hereditary hemochromatosis (HH), and later on also with transfusional iron overload.[6,7] Another study by Jiang et al in 2004 showed higher iron stores reflected by an elevated ferritin concentration are associated with an increased risk of type 2 diabetes in apparently healthy women without known diabetes risk factors.[6] In one study phlebotomy was followed by decreases in serum glucose, cholesterol, triglycerides and apoprotein B, and by improvement in both β-cell secretion and peripheral insulin action in patients with type 2 diabetes.[5,7] A recent pilot study done by Wilson MS and Thompson EW in year 2016 concluded that in patients with type 2 diabetes and also with elevated serum ferritin, venesection can be used successfully with oral pharmacotherapy, thereby avoiding the use of insulin.8 In 1997, a cross-sectional population study showed that mildly elevated serum ferritin was associated with elevated fasting serum insulin, that means persons with the higher serum ferritin needed to produce more insulin to remain normoglycemic.[9] A meta-analysis has showed that elevated levels of serum ferritin may help to identify individuals at risk of type 2 diabetes and in 2008, Le and co-workers suggested that serum ferritin concentration could be used as a predictor for diabetes.[10]

Even mildly elevated body iron stores are associated with statistically significant increases in glucose homeostasis indices.3 But till now high serum ferritin associated with type 2 diabetes is not recognized as an entity in the current clinical guidelines for the management of type 2 diabetes. The present study was thus designed to determine the hormone fasting insulin levels, fasting blood sugar levels and serum ferritin levels by standard methods and then to assess whether there is any association of insulin resistance and serum ferritin in PCOS patients. The objective of this study was to see the association of serum ferritin level with insulin resistance in PCOS women and to estimate serum ferritin level in PCOS patients.

MATERIAL AND METHODS

The current study was conducted in urban tertiary hospital based a Case-control analytic cross-sectional study in Departments of Biochemistry and Gynecology & Obstetrics of Faculty of Medicine and Health Sciences, SGT University, Budhera, Gurugram, India on 160 subjects aged between 18 to 45 years comprising of 80 healthy control and 80 patients with clinically diagnosed cases of PCOS, acted as study group. The blood samples of controls as well as study groups were withdrawn and Clinical evaluation included anthropometry, Hight, Weight, Body Mass Index (BMI) and waist-to-hip ratio (WHR) were calculated. Circulating levels of fasting glucose, insulin resistance, Serum Thyroid stimulating hormone level, Serum Ferritin level and Serum Gama amino butyric acid level were determined by Chemiluminescence based immunoassay (CLIA) on fully automated Biochemistry analyzer MAGLUMI 1000.

Inclusion criteria

Known cases of PCOS having at least two of the three following features as per Rotterdam's criteria.[12]

1. Radiologically confirmed multiple small cysts in ovary
2. Irregular menses
3. Hirsutism (acne)

Exclusion criteria

1. Patients on drugs having androgen excess
2. Patients with Androgen secretion tumour
3. Patients with Other endocrinal disorder
4. Patients on Vitamin D drugs
5. Chronic illness (Hypertension, Chronic Kidney Disease, Coronary artery disease)

Eighty BMI and age matched healthy volunteers from general population were taken as control. After explaining the purpose details of the study to all the subjects of both the groups, a written and informed consent was taken. Ethical clearance was taken from the Institutional Ethical Committee before the start of collecting the samples.

STATISTICAL ANALYSIS

Detailed data of all subjects of case and control group were collected. After complete evaluation all findings were expressed in terms of Mean ± SD. Comparison between case group and control group was done using paired "t" test. All statistical analysis was done using SPSS software version 20.

RESULTS

It is observed that the clinical and biochemical parameters of the groups studied are presented in Table. 1 and Total 160 subjects with both control and study group PCOS patients were included in the study. The age of these control group was ranged from 18 to 45 years, with a mean of 26.23±5.58 years and PCOS study were found 27.76 ±6.54 years. The findings of anthropometric measurements of the subjects of both PCOS syndrome (n=80) and non-PCOS (n=80). As expected, mean levels of BMI, Weight, Height showed marked difference and were statistically significantly increased (P<0.0001) in both the groups. The serum levels of serum Fasting blood glucose level, insulin resistance, and Serum Ferritin were significantly increased (P<0.0001) in subjects with PCOS and without PCOS compared to controls. (Table no. 1 & 2). Table-3 depicts the correlation coefficient analysis between variables of HOMA IR and Fasting blood sugar, Ferritin, TSH, GABA, BMI as well as weight in subjects with PCOS group. In the whole group, HOMA IR was correlated positively with Ferritin, TSH, BMI. HOMA IR was significantly correlated with Fasting blood sugar (r=0.679;r=0.001), Ferritin (r=0.521;r=0.02), Thyroid Stimulating Hormone (r=0.270;r=0.029), BMI (r=0.368;r=0.001), and WC (r=0.657;r=0.001) all correlation were found to be statistically significant at the 0.01 level(2-tailed). In our study, significant correlation was found between serum ferritin levels and serum insulin levels or serum glucose levels and insulin resistance in women with PCOS. Ko et al. found significant positive correlations between serum ferritin levels and serum insulin levels in addition to serum glucose levels and insulin resistance in obese women with PCOS.

Table:1 The clinical, hormonal and metabolic parameters in patients with PCOS and control women

Sr.No	Parameters	Healthy control subjects (n= 80)	Polycystic Ovarian Syndrome Subjects (n= 80)	*p*-value
1.	**Age (Years)**	26.23±5.58	27.76 ±6.54	0.45
2.	**Body Weight (Kg)**	56.87±10.75	60.59±12.36	0.0001
3.	**BMI (kg/m^2)**	22.87±2.87	26.98±5.38	0.0001

Table: 2 The clinical, hormonal and metabolic parameters in patients with PCOS and control women

Sr.No	Parameters	Healthy control subjects (n= 80)	Polycystic Ovarian Syndrome Subjects (n= 80)	Statistical Significance (p)
1.	**Fasting blood sugar (mg/dl)**	**83.12 ± 6.98**	**90.29 ± 8.33**	**0.0001**
2.	**Serum Insulin (µU/L)**	**18.76 ± 13.72**	**24.99 ± 6.93**	**0.0001**
3.	**Serum Insulin resistance HOMA IR**	**2.38 ± 1.01**	**5.56 ± 1.64**	**0.0001**
4.	**Serum Ferritin level (ng/mL)**	**42.67 ± 9.87**	**77.45 ± 19.39**	**0.0001**

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Table No. 3 Pearson Correlation Coefficient between Variables of HOMA IR with clinical, hormonal, biochemical and Anthropometric Parameters in women with Polycystic Ovarian Syndrome Subjects

S. No.	Pearson Correlated with	HOMA IR	
		r-value	Statistical Significance (p)
1.	Fasting blood sugar	0.679**	0.0001
2.	Ferritin	0.521**	0.002
3.	BMI	0.368**	0.0001
4.	WC	0.657**	0.0001

** Correlation is significant at the 0.01 level (2-tailed)
* Correlation is significant at the 0.05 level (2-tailed)
HS* - Highly Significant

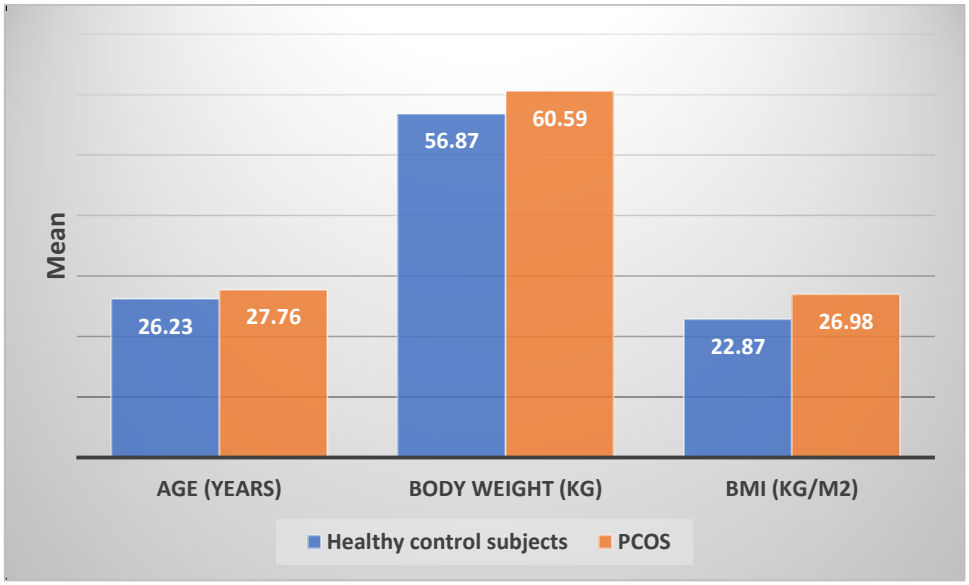

Figure: 1 Comparison of Mean±SD of Anthropometric Parameters of the Polycystic Ovarian Syndrome Subjects and without PCOS Control Subjects

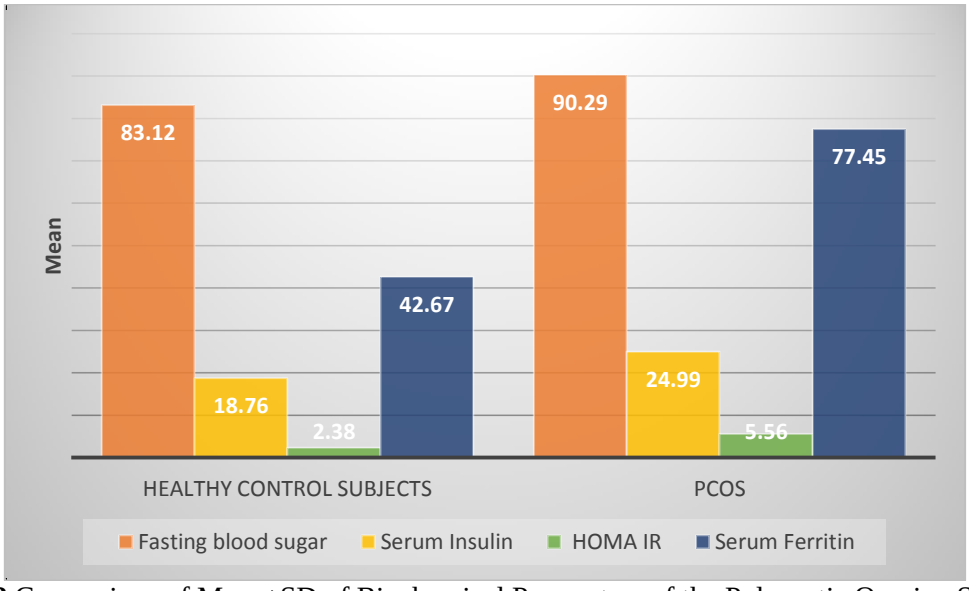

Figure: 2 Comparison of Mean±SD of Biochemical Parameters of the Polycystic Ovarian Syndrome Subjects and without PCOS Control Subjects

DISCUSSION

Our study suggested a strong association of PCOS with insulin resistance in this part of the world. The cause of hyperinsulinemia among women with PCOS remains unknown. This can be due to increase phosphorylation of insulin receptor proteins, which decreases its protein tyrosine kinase activity leading to abnormal insulin secretion.[13-15]

There are significant differences in insulin sensitivity between ovulatory and anovulatory women with PCOS. Anovulatory women with PCOS display insulin resistance whereas those with regular menstrual cycle (but who present with symptoms of hyperandrogenism) do not demonstrate insulin resistance. [16] These observations suggest that there is a strong association between menstrual irregularity and insulin resistance among women with PCOS.146 Several studies have assessed glucose tolerance among PCOS women and overall risk of developing type-2 diabetes was found to be increased 3 to 7 times.147-150

The risk of glucose intolerance in PCOS women appears to be equally increased in mixed ethnicities of US population and Asian PCOS groups.[16-19] However in young Mediterranean population, prevalence of glucose was lower. [20]

The onset of glucose intolerance in PCOS occurs at an early age typically in 3rd - 4th decade of life. 156-159Also hyperinsulinemia was found to be common among female and male 1st degree relatives of women with PCOS. [21]

In our study, insulin resistance (HOMA-IR) was found to be higher in women with PCOS than in control group. However, a statistically significant result was found only in the overweight group ($p < 0.001$). Similar to our study, Durmuş et al. it was shown that women with PCOS have higher HOMA-IR.161 To achieve insulin action in a healthy metabolism, it must bind to its specific receptor in the cell membrane and phosphorylation of tyrosine. Interestingly, however, serine phosphorylation of the insulin receptor occurs in women with PCOS, resulting in post-receptor abnormalities in insulin action. [21-24]

Association of serum ferritin with insulin resistance in polycystic ovarian syndrome. Ferritin is the cellular storage protein for iron, and reduced serum ferritin provides unequivocal evidence of diminished iron stores. In women, a serum ferritin concentration >150 ng/mL is usually defined as hyperferritinemia, but increased serum ferritin concentrations in nonpathological conditions, reflecting subclinical iron overload, are associated with insulin resistance and an increased risk of type 2 diabetes mellitus. [25-29]This is probably due to the fact that the normal ranges of serum ferritin are too wide, and the criteria for iron overload are too high.[30]

This study also aimed to determine the association between serum ferritin level and insulin resistance in women with PCOS. In the present study serum ferritin level is found to be associated with insulin resistance in women with PCOS. Previous findings suggest there is a relationship between iron overload and the development of insulin resistance. The central role of iron in biology can be understood by the fact that iron is the fourth most abundant element in Earth's crust as well as the transition element, most abundant in all living organisms including human being. Iron induced cell oxidative stress can explain some extent of its association with abnormal insulin sensitivity. [31-34]

CONCLUSIONS

We conclude that PCOS women with infertility was studied regarding insulin resistance and serum ferritin level. Most of the PCOS patients were in 3rd decade, either overweight or obese having central obesity. Significantly increased fasting insulin level, HOMA-IR, and insulin resistant cases were reported in PCOS patients with high ferritin level. Significantly increased serum ferritin was found in insulin resistance cases. Statistically significant strong positive correlation was observed between serum ferritin and fasting insulin as well as between serum ferritin and HOMA IR. These results demonstrated that elevated level of serum ferritin was associated with insulin resistance in PCOS women. Further research is encouraged to determine the efficacy of applying these biomarkers to diagnosis and treatment in a clinical setting.

DISCLOSURE STATEMENT

This study is investigator initiated. The authors declare that they have no competing/conflict of interests in relation to this article.

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CONSENT FOR PUBLICATION
Not applicable.
Ethics approval and consent to participate.

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